PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 10002	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/013549	International filing date *(day/month/year)* 29 November 2004 (29.11.2004)	Priority date *(day/month/year)* 19 January 2004 (19.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant HUYBRECHTS, Lucas		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 24 July 2006 (24.07.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

REC'D 08 AUG 2005
WIPO PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/013549	International filing date *(day/month/year)* 29.11.2004
Priority date *(day/month/year)* 19.01.2004	
International Patent Classification (IPC) or both national classification and IPC C07K14/47, C07K14/00, A61K6/033, A61K7/16	
Applicant HUYBRECHTS, Lucas	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/013549

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially); 3-5,8,26,27 as to IA

because:

☒ the said international application, or the said claims Nos. 3-5,8,26,27 (as to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 5,8,17-24 (completely) and 1,3,4,26,27 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8
	No:	Claims	1,3-5,17-24,26,27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,3-5,8,17-24,26,27
Industrial applicability (IA)	Yes:	Claims	1,17-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 3-5,8,26 and 27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Due to an objection against unity of invention (see below), a search has been performed for subject-matter of claims 5,8,17-24 (completely) and 1,3,4,26,27 (partially) only. Therefore, no opinion on novelty, inventive step and industrial applicability will be formulated for subject-matter of claims 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially).

Re Item IV.

The separate inventions/groups of inventions are:

I: claims: 5,8,17-24 (completely) and 1,3,4,26,27 (partially)
bisphosphonylated-epsilon-polylysine, methods and uses thereof; use of proteins that are bisphosphonylated and use of epsilon-polylysine or polylysine

II: claims: 12,13 (completely) and 1,3,4,26,27 (partially)
casein phosphopeptide epsilon-polylysine copolymer, methods and uses thereof

III: claims: 16 (completely) and 1,3,4,26,27 (partially)
hydrolyzed phosvitin that has been conjugated to epsilon-polylysine, methods and uses thereof

IV: claims: 10,11 (completely) and 1,3,4,26,27 (partially)
casein phosphopeptide that has been polymerized with a carbodiimide, methods thereof

V: claims: 6,7 (completely) and 1,3,4,26,27 (partially)
phosvitin that has been hydrolyzed with trypsin, pepsin or a combination of both, methods and uses thereof

VI: claims: 2,9,14,15 (completely) and 3,4,26,27 (partially)
chitosan hydrolysate that has been conjugated with casein phosphopeptide, methods and uses thereof; use of copolymers containing hydrolyzed chitosan

VII: claim 25 (completely) and 3,4,26,27 (partially)
use of biscarboxylated epsilon-polylysine, 3-hydroxy-phthalated epsilon-polylysine or proteins that are biscarboxylated; method to produce 3-hydroxy-phthalated epsilon-polylysine

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
The problem underlying the present application is the provision of compounds for the treatment and prevention of caries.
As a solution, peptides are used that contain phosphate- or phosphonate groups.
The technical feature which a priori could unify different solutions is the entity of being a peptide containing phosphate- or phosphonate groups.
However, such a solution has already been proposed in the prior art, see e.g. the international patent application WO 02/094204 disclosing complexes of casein phosphopeptides and amorphous calcium phosphate exerting anticariogenic properties (see pages 1 and 2), or the Japanese patent application JP5310544 describing the use of epsilon-polylysine and its phosphate salts which are useful in treatment of dental caries.
The problem to be solved may therefore considered to be the provision of further peptides contain phosphate- or phosphonate groups.
However, a structural relationship between the phosphatylated or phosphonylated peptides of the different subjects which could fulfil the role of a "special technical feature" in the sense of Rule 13 PCT is missing.
As there are no other special technical features, unity of invention is lacking, giving rise to the subjects as above.

Re Item V.

Reference is made to the following documents:

D1: WO 02/103004 A (LEVY, ROBERT, J; ALFERIEV, IVAN; FISHBEIN, ILIA) 27 December 2002 (2002-12-27)

D2: PATENT ABSTRACTS OF JAPAN vol. 018, no. 118 (C-1172), 25 February 1994 (1994-02-25) & JP 05 310544 A (CHISSO CORP), 22 November 1993 (1993-11-22)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 3 is not new in the sense of Article 33(2) PCT.

The document D1 discloses (the references in parentheses applying to this document): polylysine modified with bisphosphonate as chelating group for metals (see page 8).
Therefore, subject-matter of claim 1 does not meet the requirements of Article 33(2) PCT.

The document D2 discloses the use of epsilon-polylysine having anticariogenic properties (see abstract).
Therefore, subject-matter of claim 3 does not meet the requirements of Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 8 does not involve an inventive step in the sense of Article 33(3) PCT.
The document D2 is regarded as being the closest prior art to the subject-matter of claim 8 and discloses phosphate salts of epsilon-polylysine for treatment and prevention of caries.
The subject-matter of claim 8 therefore differs from D2 in that the epsilon-polylysine is bisphosphonylated.
The problem to be solved by the present invention may therefore be regarded as a further modified form of epsilon-polylysine for treatment or prevention of caries.
The solution proposed in claim 8 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), since phosphonylation is merely one of

several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to be able to form a complex with calcium, in particular with view to the document D1 that discloses polylysine modified with bisphosphonyl groups as chelating group for metals.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 17,18,24,26 which therefore are also considered not new and/or inventive.

Dependent claims 4,5,19-23 and 27 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D1 and D2 and the corresponding passages cited in the search report.

For the assessment of the present claims 3-5,8,26 and 27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

12 Sep. 05

Dr L.Huybrechts
mina telghuislaan 9
2550 Kontich
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Kontich, September 1th 2005

To International Bureau of WIPO
34 Chemin des Colombettes
1211 Geneva 20
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Regarding : PCT/EP2004/013549 (Int. appl. number)
WO 2005/068645 A2 (Int. publ. number)
Referring to the written opinion of the international searching authority
(date of mailing: 9-8-2005)

Dear Mrs., Sir,

Please find enclosed comments from the applicant on the written opinion of the ISA (PCT rule 43 bis 1):

Summary

The examinator, author of the Opinion Report concludes that the application contains multiple groups of inventions and that there is no inventive step on the basis of prior art that claims the use of e-polylysine (JP 05 310544 A) and Casein phosphopeptide (WO 02/094204 A) as anticavity agent and on the basis that bisphosphonylated polylysines are known (WO 02/103004) in the prior art already.

The applicant argues, with inclusion of experimental data, that experts in the field of "organic synthesis" and/or "anticavity protection" are unable to predict the superior anticavity competence of the subjects of the invention (eg bisphosphonylated e-polylysine) on the basis of (JP 05 310544 A), (WO02/094204 A) and (WO 02/103004) and that the production procedure that has been described in (WO 02/103004) does not work, nor does it deliver bisphosphosphonylated e-polylysine with enhanced anticavity protection competence in comparison to non-modified e-polylysine. The applicant was obliged to discover another inventive production procedure. Therefore the subjects of the application (product and production procedure) have an inventive step.

Opinion regarding "lack of unity of invention"

The applicant appreciates that there is a lack of unity. Concequently the claims will be reformulated, and substantially reduced in order to create the required unity.

The examinator found VII different (groups of) inventions, all identified in the Written Opinion of the examinator.
However, the applicant is of the opinion that unity can be requested between groups I, II and VII.

Indeed, the problem underlying the present application is the provision of compounds for the prophylactic prevention of caries (not "treatment of illness"). The examinator states the following: "as a solution, peptides are used that contain phosphate-or phosphonate groups". However the applicant argues that the solution can be defined as "Basic proteins (and peptides) that contain at least 40% lysine amino acids and that are conjugated with calcium complexating components"; therefore "Basic proteins with at least 40% lysine amino acids that are conjugated with calcium complexating components" and more in particular "epsilon-polylysine that is conjugated with calcium complexating components" would be the unifying factor. As such, the subject of group VII:(biscarboxylated basic proteins - including e-polylysine) would be unified with group I (bisphophonylated proteins including e-polylysine) and group II (epsilon polylysine conjugated with casein phosphopeptide). The conjugation of bisphosphonyl and biscarboxyl groups to proteins (and in particular e-polylysine) for prophylactic anticavity use, is novel. It is evident that substitution of a limited number of lysine amino acids from e-polylysine does not eliminate the anticavity competence, because the required buffering competence would be available still. For this reason, we apply for unity under the term "Modified proteins that contain at least 40% lysine", rather than under "Modified e-polylysine" alone.

By using several different calcium complexing components, we have discovered that addition of such components to" proteins as have been defined" delivers anticavity competence, as a general rule. Hence, we wish also to claim biscarboxylated proteins, as biscarboxylated and bisphosphonylated components have very similar calcium complexing properties and experimental data identified the anticavity competence of both of them. It is evident that biscarboxylation of said proteins provides anticavity competence similar to bisphosphonylated proteins. Investment in patent protection of a bisphosphonylated component only would be difficult to justify as the competition would evidently develop the biscarboxylated alternative. An additional search effort on the subject of "biscarboxylated proteins (peptides) with at least 40% lysines" and in particular on "biscarboxylated e-polylysine" would be required.

Concequently, the applicant argues to retain the following products in the claims:

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1. Proteins and peptides containing at least 40% of lysine amino acids, and that have been conjugate with a calcium complexing component, selected from the group containing bisphosphonyl, biscarboxyl and casein phosphopeptide components.
2. Bisphosphonylated (e)-polylysine.
3. Biscarboxylated (e)-polylysine.
4. Casein phosphopeptide epsilon polylysine copolymer.

The following products will be removed from the claims:

hydroxyphthalated epsilon polylysine
polymerised casein phosphopeptide (CPP)n
partially hydrolysed phosvitin (phos-h)
copolymers of hydrolysed phosvitin or phosvitin with e-polylysine or with hydrolysed chitosan
bisphosphonylated hydrolysed chitosan (bispho x hy chit)
casein phosphopeptide hydrolysed chitosan copolymer (CPP x hy chit)n

The product claim (part of claim 1) regarding bisphosphonylated e-polylysine, is retained.

The applicant discovered by experimental means that it is not possible to use the procedure that is mentioned in WO 02/103004 for the production of bisphosphonylated e-polylysine without substantial degradation. The term bisphosphonylated e-polylysine preferably is understood in the field of chemistry as bisphosphonylated polylysine without severe degradation of the peptide backbone. In addition it is not possible to produce the products of this invention, in particular 2-e-polylysine-1-hydroxyethane-1,1 diphosphonate with the procedure from WO 02/103004.

The applicant argues to keep also the claim 5 (original number) (partially) in the application regarding the prophylactic use of e-polylysine against halitosis. Indeed novelty is claimed only and the prior art is only available regarding "use against caries and parodontitis", not against halitosis (ref. JP05 310544). Halitosis (generation of bad breath by anaerobic bacterien residing especially on the tongue; ref. J Clin Periodontol. 2003 Dec;30(12):1017-23. ; D.Hinode et al) is not the same illness as parodontitis (regression of flesh surrounding the teeth due to toxin production by local bacteria and immunological response, resulting in the loss of teeth). Many people have parodontitis without halitosis and vice versa. Patent JP05 310544 refers to the use of e-polylysine, as antimicrobial agent against parodontitis. It is substantiated with the claim that e-polylysine acts against streptococcus mutans; however, this does not suggest efficacity against the bacteria that cause halitosis. Many peptides exists, including cationic (antimicrobial) peptides, that do not act against halitosis, such as lyzozym, lactoferrin and nisin. The applicant has been the first to discover by experimental means the excellent activity of e-polylysine against halitosis and has been the first to, surprisingly, discover the selectivity of it's action against anaerobes (at constant dosage it blocks growth of 70% of oral anaerobes and only of 11% of oral aerobes; for ref. you may consult fig. 4 and 7 in the application WO2005/068645). For this the applicant has invested considerably in the hope to demonstrate e-polylysine's action against (some of) over 120 different organisms, all sourced from the oral cavity.

Opinion regarding novelty

The applicant claims novelty for the use as prophylactic anticavity products of all of the claimed products, and for the production of bisphosphonylated e-polylysine. An additional search regarding use of biscarboxylated proteins with more than 40% lysine amino acids (or biscarboxylated e-polylysine) , would be required.

The applicants claims novelty also for the use of e-polylysine specifically against halitosis; an additional search would be required.

Opinion regarding inventive step in "product use" claims

The applicant does not share the opinion of the examinator that there is no inventive step. The examinator refers to 3 documents of "suggested prior art" and claims that the existence of prior art concerning the use of e-polylysine as an antimicrobial anticavity agent (especially in the phosphate salt form) and of prior art concerning the use of anticavity casein phosphate peptides (CPP) that complex calcium ions, is sufficient reason to conclude that the development of claimed products are "evident" and hence without inventive step.

It is important to note that the anticavity competence of the prior art products, e-polylysine (JP 05 310544 A) and CPP (WO 02/094204A) is said (in the prior art documents) to originate from a completely different property; e-polylysine is said to act as an antibacterial product and CPP as a component that complexes calcium ions that exist in the solution, for keeping them available for repair work on the tooth surface.

It is also important to note that the products of this patent application, such as "modified e-polylysine" that has been conjugated with bisphosphonyl, casein phosphopeptide, hydroxyphthalate or biscarboxyl groups, provides superior prophylactic anticavity competence in comparison to the products of the prior art, such as e-polylysine and casein phosphopeptides (ref. patent application WO2005/068645; in-vitro experiments no. 2 and 3 and especially in-vivo experiment C.2.2.).

The applicant claims that no information whatsoever is available in the so-called "prior art documents" that may suggest or assume the superiority of the products of WO2005/068645 over the competitive products.

In particular,
Patent WO 02/094204A claims the use of "casein phosphopeptides that complex with calcium ions " as anticavity products. It is important to realize that the presence of phosphate or phoshonate in a random way (either as a salt or in mono-conjugated form) does not contribute to providing calcium complexation competence. For this to achieve, a specific structural arrangement of a least two anionic (possibly phosphate) groups must be present in the protein; the nature of this structure in CPP is not known. The use of phosphates (or phosphonates) randomly attached to a polymer (or peptide) or in the form of a salt does not provide any anticavity competence (as an example the applicant has developed randomly phosphonylated chitosan that exhibits no anticavity competence (data are not included in the application, but data for carboxylated chitosan are, exp. 3. page 31) . Hence the random conjugation or presence of phosphates (phosphonates) to peptides is not relevant and does not deliver the desired protection competence.

The applicant recognizes that the use of a calcium complexing agent "as such" is not novel; but patent WO 02/094204A does not contain information that allows to predict or assume that the use of bisphosphonyl or biscarboxyl groups, instead of the "normal & natural" calcium complexating units of unknown structure in CPP, actually would improve the anticavity competence of the product. In addition, this document does not contain any information that allows the expert to predict or assume that the replacement of casein proteins with proteins that contains large amounts of lysine amino acids (or in particular with e-polylysine) in the conjugation with calcium complexing components, would actually improve the anticavity competence of the product. Indeed, WO 02/094204A claims an anticavity competence on the basis of complexation of CPP with calcium ions from the solution, keeping these ions available for repair work on the tooth surface. There is no theoretical basis, for experts in this field, to assume or predict that the use of a basic protein (such as e-polylysine) in replacement of the non-basic CPP peptide, would actually improve the complexation of calcium ions in solution in such a way that the anticavity competence would increase. Since, surprisingly, the anticavity competence of bisphosphonylated, biscarboxylated polylysines and other appear superior to CPP, it indicates that factors, other than complexation of calcium ions, factors that are not mentioned in WO 02/094204A, play a role in the creation of superior anticavity products. In other words, how can the information about phosphated peptides such as CPP that make a complex with calcium ions, allow the prediction that addition of bisphosphonylated components especially to basic proteins (with lysine) would provide improved and superior anticavity competence in comparison to products from WO 02/094204A? It cannot. Therefore this document does not provide prior art to the surprising finding that the products of the application WO2005/068645 are superior in comparison to the products of WO 02/094204A.

The presence of invented step is further substantiated by the fact that the authors of WO 02/094204A did not develop themselves the superior products from the invention of WO2005/068645; if the development of the products of the applicant would be "evident" and would not require the inventive step, the authors of WO 02/094204A would have done so.

This is further substantiated by the fact that many other type of products have been developed by the applicant (ref. the patent application WO2005/068645: phosvitin, degraged phosvitin, polymerized CPP.....) before the most superior products could be identified, suggesting that the development of the superior bisphosphonylated peptides (containing lysine) was not "obvious" nor "evident" on the basis of prior art information and only discovered by accident in the course of production of many different types of products.

Patent JP 05 310544 A claims the use of e-polyslyine as anticavity product purely on the basis of its antimicrobial competence. It can be used in free form as well as in many different types of salt form (one of which is phosphate salt). The presence of phosphate salt (or of mono conjugate phosphate) does not contribute to the anticavity competence. Other forms, including the non-salt forms, of polylysine are equally effective. The applicant holds experimental proof (only partly included in patent application WO2005/068645 - page 31) that phosphonylation or carboxylation of basic polymers such as chitosan does not provide anticavity competence whatsoever; the presence of phosphate salt or mono conjugated phosphate is not relevant therefore in this respect.
The patent JP 05 310544 A does not contain information that allows an expert in the field to predict or assume that bisphosphonylation of e-polylysine would increase the anticavity competence. In fact, the contrary is true; patent JP 05 310544 is referring solely to the antimicrobial competence of the peptide as the source of its anticavity competence and...it appears that conjugation of e-polylysine with bisphosphonyl groups actually **reduces** the antimicrobial effect instead than to improve it (ref. the patent application WO2005/068645 fig. 4 to 8; this is the case for anaerobic, aerobic and microaerophilic bacteria but in particular also for fungi). Hence JP 05 310544 is rather discouraging the applicant from attaching such groups to e-polylysine. Nothwithstanding, the applicant has surprisingly discovered that bisphosphonylation of e-polylysine improves the anticavity competence suggesting that factors, other than microbial competence, play a role and such factors have not been mentioned in patent JP 05 310544 In other words, how can the information about the antimicrobial competence of e-polylysine (phosphate salt) that provides some limited anticavity protection (in our patent application: the in-vivo test with e-polylysine is not statistically significant; ref. application C.2.2 column E in table on page 36) suggest that addition of bisphosphonyl groups would actually improve the anticavity competence ? It cannot, even not in the presence of the information of patent 02/094204A which is solely referring to "complexation with calcium ions in solution", a competence that e-polylysine fails to have.
To the conclusion of the applicant, the claimed products of WO 2005/068645 are superior to prior art products and none of the prior art patents contains information that allows an expert in this field to predict that the claimed products have superior prophylactic anticavity competence compared to prior art products. For this the applicant is of theopinion that there is "inventive step".

The examinator also refers to patent WO 02/103004 which claims the use of bisphosphonylated polylysine for complexating with metal plates of medical devises, used to introduce active molecules in mamalian cells. As such he claims evidence for the use of said product in complexation of metals.

However "polylysine", the product name that is mentioned in WO 02/103004, does not have the same structure as "epsilon polylysine" which is claimed in our patent application WO 2005/068645.
In addition WO 02/103004 does not contain information that allows for an expert to predict that e-polylysine or polylysine which is conjugated to bisphosphonyl components, likely has superior anticavity properties over competitive products such as e-polylysine or casein phosphopeptide. There is no theoretical basis on which such conclusion can be taken from beforehand. It is just another market, another application, another use..complexation of metal devices does not require the same competence as tooth protection.

In addition, the applicant has experimental proof that the production procedure for bisphosphophonylated e-polylysine as decribed in WO 02/103004 does not work. Based on our experience with e-polylysine we can factly conclude that the peptide is not very stable (as most peptides) and cannot stand temperatures above 50°C, especially not under basic pH conditions. According to our experience such conditions lead to degraded,denaturated and unsoluble polylysines (due to inter- and intramolecular coupling with activated nitrogen-atoms). In prior art WO 02/103004 temperatures between 115 and 120 °C are used over a long time period. It is interesting to note that only "carbon atom based" polyallylamines are used in the examples of WO 02/103004 and no peptides. It is also noteworthy that the products of WO 02/103004 dissolve only slowly in water and only under highly basic conditions (pH > 10); such conditions do not favour it's use in oral care products as the high pH that is required to keep the peptide in solution, would irritate the oral cavity. The applicant has tried to produce bisphosphonylated e-polylysine according to the procedures of WO 02/103004 but without success. The removal of water, in this procedure, prohibts good conjugation between the polylysine and the bisphosphonate components, and provides a product with an anticavity competence that is equal to the one of e-polylysine and much less compared to the one of a bisphosphonylated e-polylsine that has been made according to the procedure of this application WO 2005/068645 (PF factor respectively 55 and 99 for bisphosphonylated e-polylysine produced according to the method from WO 02/103004 and WO 2005/068645; for definition of PF factor see WO 2005/068645). In addition the procedure of WO 02/103004 leads to enhanced losses during purification on ultrafiltration equipment, possibly due to degradation of the peptide at such a high temperature (yield is 50% only of amount of used e-polylysine). The procedure of WO 2005/068645 provides products at substantially higher yield.
The direct addition of a nucleophile to a vinylidene compound is normally carried out only on "activated vinylidene's"; non-activated vinylidene compounds (this is , without the presence of electron reducing components) are densely populated with electrons and require a high temperature for reaction with a nucleophile. This is not advisable for use with relative unstable products such as peptides.
In conclusion, the procedure of prior art patent WO 02/103004 cannot be used for this application, does not provide products with good anticavity competence and the applicant was obliged to discover another production procedure.

Opinon regarding inventive steps in the production procedure claims
The examinator concludes that there is no inventive step in the procedure claims for production of bisphosphonylated e-polylysine from e-polylysine and a bisphosphonylated epoxide.
The applicant appreciates that the addition of a nitrogen atom to an epoxide and subsequent ring-opening is not new.

However all the available prior art is about the addition of epoxides to "small" molecules (for example ammonia - US 3957858), not to polymers, especially not to polymers that are relatively unstable such as peptides. On the basis of the prior it cannot be predicted by experts in the field whether or not such conjugation to e-polylysine would provide undegraded bisphosphonylated e-polylysine. The unstable peptide may denaturate, crosslink in an inter- or intramolecular way, degrade and/or become insoluble in water.
In fact the applicant has carried out the procedure under many varying circumstances and often the e-polylysine appeared to have been degraded, denaturated and crosslinked into a product that cannot be analysed anymore and that does not dissolve anymore in water or organic solvent. Secondly, the aim is to add more than one bisphosphonyl component to e-polylysine; this is often difficult to achieve due to strong repulsion forces between the anionic groups of the bisphosphonylated components.
Only by exploring many different production parameters, the applicant was able to discover by surprise a set of conditions under which the epsilon polylysine could be bisphosphonylated with multiple units, without serious degradation and yielding a new peptide that is still soluble in water. Peptides provide a special challenge to such type of reaction and the outcome could not be predicted by experts...and often failed. Therefore, we believe, the discovered reaction conditions and production procedure holds an inventive step.
This is especially the case for the procedure that includes the use of "denaturated" e-polylysine; the concept of using a denaturated polylysine in order to improve the bisphosphonylation has not been described in any prior art according to the knowledge of the applicant. It has an inventive step.

In case the examinator is of the opinion that there is no invented step in WO 2005/068645 and that the discovery is evident , it would be helpful if he would identify the text and sentences in the prior art documents that supposedly eliminate the invented step.

On the basis of the changes in the claims (to provide unity) and on the basis of the delivered arguments, the applicant requests for a reconsideration. Indeed there is no prior art available on the basis of which an expert in this field can reasonable assume or predict that the products of this application WO 2005/068645 have superior anticavity competence than the products from the prior art (JP 05 310544 A), (WO02/094204 A) and (WO 02/103004). The applicant trusts that the authority will come to fair and objective conclusions. And we hope that substantial attention and reconsideration will be provided, as the survival of the company, which is created for this technology, is entirely dependant on the granting of this patent.

With kind regards

Dr L.Huybrechts

A copy has been sent to Mr. Harald Schmidt, ISA, European Patent Office, PB 5818 Patentlaan 2, NL 2280 HV Rijswijk , The Netherlands

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/013549	International filing date *(day/month/year)* 29.11.2004
Priority date *(day/month/year)* 19.01.2004	
International Patent Classification (IPC) or both national classification and IPC C07K14/47, C07K14/00, A61K6/033, A61K7/16	
Applicant HUYBRECHTS, Lucas	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially); 3-5,8,26,27 as to IA

because:

☒ the said international application, or the said claims Nos. 3-5,8,26,27 (as to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 5,8,17-24 (completely) and 1,3,4,26,27 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8
	No:	Claims	1,3-5,17-24,26,27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,3-5,8,17-24,26,27
Industrial applicability (IA)	Yes:	Claims	1,17-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 3-5,8,26 and 27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Due to an objection against unity of invention (see below), a search has been performed for subject-matter of claims 5,8,17-24 (completely) and 1,3,4,26,27 (partially) only. Therefore, no opinion on novelty, inventive step and industrial applicability will be formulated for subject-matter of claims 2,6,7,9-16,25 (completely) and 1,3,4,26,27 (partially).

Re Item IV.

The separate inventions/groups of inventions are:

I: claims: 5,8,17-24 (completely) and 1,3,4,26,27 (partially)
bisphosphonylated-epsilon-polylysine, methods and uses thereof; use of proteins that are bisphosphonylated and use of epsilon-polylysine or polylysine

II: claims: 12,13 (completely) and 1,3,4,26,27 (partially)
casein phosphopeptide epsilon-polylysine copolymer, methods and uses thereof

III: claims: 16 (completely) and 1,3,4,26,27 (partially)
hydrolyzed phosvitin that has been conjugated to epsilon-polylysine, methods and uses thereof

IV: claims: 10,11 (completely) and 1,3,4,26,27 (partially)
casein phosphopeptide that has been polymerized with a carbodiimide, methods thereof

V: claims: 6,7 (completely) and 1,3,4,26,27 (partially)
phosvitin that has been hydrolyzed with trypsin, pepsin or a combination of both, methods and uses thereof

VI: claims: 2,9,14,15 (completely) and 3,4,26,27 (partially)
chitosan hydrolysate that has been conjugated with casein phosphopeptide, methods and uses thereof; use of copolymers containing hydrolyzed chitosan

VII: claim 25 (completely) and 3,4,26,27 (partially)
use of biscarboxylated epsilon-polylysine, 3-hydroxy-phthalated epsilon-polylysine or proteins that are biscarboxylated; method to produce 3-hydroxy-phthalated epsilon-polylysine

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
The problem underlying the present application is the provision of compounds for the treatment and prevention of caries.
As a solution, peptides are used that contain phosphate- or phosphonate groups.
The technical feature which a priori could unify different solutions is the entity of being a peptide containing phosphate- or phosphonate groups.
However, such a solution has already been proposed in the prior art, see e.g. the international patent application WO 02/094204 disclosing complexes of casein phosphopeptides and amorphous calcium phosphate exerting anticariogenic properties (see pages 1 and 2), or the Japanese patent application JP5310544 describing the use of epsilon-polylysine and its phosphate salts which are useful in treatment of dental caries.
The problem to be solved may therefore considered to be the provision of further peptides contain phosphate- or phosphonate groups.
However, a structural relationship between the phosphatylated or phosphonylated peptides of the different subjects which could fulfil the role of a "special technical feature" in the sense of Rule 13 PCT is missing.
As there are no other special technical features, unity of invention is lacking, giving rise to the subjects as above.

Re Item V.

Reference is made to the following documents:

D1: WO 02/103004 A (LEVY, ROBERT, J; ALFERIEV, IVAN; FISHBEIN, ILIA) 27 December 2002 (2002-12-27)

D2: PATENT ABSTRACTS OF JAPAN vol. 018, no. 118 (C-1172), 25 February 1994 (1994-02-25) & JP 05 310544 A (CHISSO CORP), 22 November 1993 (1993-11-22)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 3 is not new in the sense of Article 33(2) PCT.

The document D1 discloses (the references in parentheses applying to this document): polylysine modified with bisphosphonate as chelating group for metals (see page 8).
Therefore, subject-matter of claim 1 does not meet the requirements of Article 33(2) PCT.

The document D2 discloses the use of epsilon-polylysine having anticariogenic properties (see abstract).
Therefore, subject-matter of claim 3 does not meet the requirements of Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 8 does not involve an inventive step in the sense of Article 33(3) PCT.
The document D2 is regarded as being the closest prior art to the subject-matter of claim 8 and discloses phosphate salts of epsilon-polylysine for treatment and prevention of caries.
The subject-matter of claim 8 therefore differs from D2 in that the epsilon-polylysine is bisphosphonylated.
The problem to be solved by the present invention may therefore be regarded as a further modified form of epsilon-polylysine for treatment or prevention of caries.
The solution proposed in claim 8 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), since phosphonylation is merely one of

several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to be able to form a complex with calcium, in particular with view to the document D1 that discloses polylysine modified with bisphosphonyl groups as chelating group for metals.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 17,18,24,26 which therefore are also considered not new and/or inventive.

Dependent claims 4,5,19-23 and 27 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D1 and D2 and the corresponding passages cited in the search report.

For the assessment of the present claims 3-5,8,26 and 27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.